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Scleroderma: Nomenclature, etiology, pathogenesis, prognosis, and treatments: Facts and controversies

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Abstract *Scleroderma* refers to a heterogeneous group of autoimmune fibrosing disorders. The nomenclature of scleroderma has changed dramatically in recent years, with morphea (localized scleroderma), limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, and systemic sclerosis sine scleroderma encompassing the currently accepted disease subtypes. Major advances have been made in the molecular studies of morphea and systemic sclerosis; however, their etiologies and pathogenesis remain incompletely understood. Although morphea and systemic sclerosis demonstrate activation of similar inflammatory and fibrotic pathways, important differences in signaling pathways and gene signatures indicate they are likely biologically distinct processes. Morphea can cause significant morbidity but does not affect mortality, whereas systemic sclerosis has the highest disease-specific mortality of all autoimmune connective tissue diseases. Treatment recommendations for morphea and systemic sclerosis are based on limited data and largely expert opinions. Current collaborative efforts in morphea and systemic sclerosis research will hopefully lead to better understanding of the etiology and pathogenesis of these rare and varied diseases and improved treatment options.
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What is in a name?

Scleroderma is a disease label fraught with misunderstandings. In recent years, the nomenclature of scleroderma has been replaced by more precise terminology, characterizing disease subsets defined by clinical findings, serologic data, and prognosis. The subsets include localized scleroderma (ie, morphea), limited cutaneous systemic sclerosis (LcSSc; previously referred to as CREST syndrome), diffuse cutaneous systemic sclerosis (DcSSc), and systemic sclerosis sine scleroderma. Experts in the field of adult localized scleroderma prefer to refer to this clinical entity as morphea, to decrease miscommunication with patients and referring physicians (patients and doctors alike hear *scleroderma* and assume the diagnosis is systemic sclerosis, which leads to unnecessary stress). In general, experts in the field of pediatric localized scleroderma prefer to keep the scleroderma moniker to stress the morbidity associated with the linear variants of this disease in their patient population.

Patients with LcSSc and DcSSc almost universally will have positive antinuclear antibodies (ANA), Raynaud's phenomenon, and nailfold capillary changes.[1,2] Patients with LcSSc develop sclerosis of the skin distal to their elbows and knees and have facial involvement. Patients with DcSSc develop proximal, in addition to distal, sclerosis. Patients with LcSSc are more likely to have anti-centromere antibodies, whereas patients with DcSSc are more likely to have anti-topoisomerase I (anti-Scl70) or anti-RNA polymerase III antibodies.[1,2] Patients with LcSSc and DcSSc are

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approximately equally likely to develop interstitial lung disease (ILD), but patients with LcSSc are at higher risk for fibrosis of their pulmonary artery leading to pulmonary artery hypertension (PAH).[1,2] Patients with DcSSc are at higher risk for renal crisis than their LcSSc counterparts.[1,2]

Morphea is a diverse disease as well, with distinct clinical presentations: circumscribed morphea (with superficial and deep variants), linear morphea (with trunk/limb variant and head variant), generalized morphea, pansclerotic morphea, and mixed morphea.[3] Linear morphea is more likely to affect children and involve underlying structures including soft tissue, bone, and when on the head and neck, the central nervous system.[3] Patients with generalized morphea are more likely to have positive autoantibodies and systemic symptoms including myalgia, arthralgia, and fatigue.[3–6] To date, no studies have assessed the differences in the pathophysiology of morphea subtypes.

Etiology and pathogenesis: Are morphea and systemic sclerosis the same disease on one continuous spectrum, or separate diseases?

The etiologies and pathogenesis of morphea and systemic sclerosis are incompletely understood at this time. A combination of factors is postulated to be involved. It is currently thought that patients who develop morphea or systemic sclerosis have an underlying genetic predisposition to these conditions, and then are exposed to an environmental factor that initiates the inflammatory and fibrotic cascades. To date, no studies on specific genetic alterations have been performed in morphea; however, patients with morphea have higher rates of autoimmune diseases in their families than expected in the general population.[3,5,7] Several large genome-wide association studies have been performed in patients with systemic sclerosis revealing association of systemic sclerosis with multiple genetic loci including HLA class II gene region, *IRF5, CD247, BANK1, STAT4, TNFSF4,* and *BLK* genes.[8] For a comprehensive review of these studies, please see Romano et al.[8]

In morphea, several environmental factors have been postulated to be part of the etiology, including Lyme disease, trauma, radiation, medications, and viral infections.[9] Of these, radiation-induced morphea is most frequently described. Morphea occurs commonly on the chest wall after radiation treatment for breast cancer, with an estimated incidence of 1 in 500 patients.[9–11] The role of radiation in the induction of morphea is not completely understood. It has been postulated that radiation selects for activated fibroblasts, or induces an isomorphic response due to tissue trauma, or may increase the risk for presentation of self-antigens. In systemic sclerosis, postulated environmental factors include exposure to vinyl chloride, silica dust and organic solvents, medications (bleomycin, pentazocine, cocaine), and viruses (cytomegalovirus, parvovirus B19).[2,9]

The combination of genetics and a second environmental "hit" is thought to cause endothelial cell injury, resulting in up-regulation of cellular adhesion molecules (VCAM, ICAM, E-selectin) and chemokines (CCL2,5,7,17,22,27, CXCL8).[12,13] The cellular adhesion molecules and chemokines recruit inflammatory mononuclear cells, of which most are T-helper (Th) cells. The Th cells (Th1, Th2, and Th17) produce interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, IL-12, IL-13, IL-17, tumor necrosis factor (TNF)-α, interferon (IFN)-α and IFn-γ.[2,14,15] Production of these cytokines results in inflammation, and recruitment and activation of fibroblasts and myofibroblasts, resulting in fibrosis.[12,16,17] Kurzinski et al. postulate that the initial inflammatory phase is mediated by Th1 and Th17 cells and their associated cytokine profiles, with a shift in predominant cell phenotype to Th2 cells later in disease course, which results in sclerosis.[14]

Despite several shared pathogenic features, clinically morphea and systemic sclerosis are radically different diseases. The explanation for this distinct clinical disparity despite similar molecular pathogenic pathways remains unsolved. The following are pathogenic disparities between morphea and systemic sclerosis.

In a single study comparing subjects with morphea and systemic sclerosis, subjects with morphea were found to have higher levels of IL-2 and IL-6.[18]In an additional study comparing the effect of peripheral blood mononuclear cells (PBMC) from subjects with morphea and systemic sclerosis on cultured fibroblasts, the PBMCs from subjects with systemic sclerosis caused a decrease in matrix metalloproteinase-1 (a collagenase) and an increase in platelet-derived growth factor AA and BB, TNF-α, IL-13, and epidermal growth factor compared with those subjects with morphea.[19]

Autoantibody production is also disparate in morphea and systemic sclerosis. Greater than 95% of patients with systemic sclerosis will have a positive ANA,[2,20–22] whereas prevalences of ANA positivity in patients with morphea range from 20% to 80.[3–5,23–25] Anti-centromere antibodies, anti-topoisomerase I antibodies, and anti-RNA polymerase III antibodies are found almost exclusively in patients with systemic sclerosis.[2,224] In contrast, patients with morphea are more likely to have anti-single–stranded antibodies, anti-histone antibodies, and anti-topoisomerase II-α antibodies than patients with systemic sclerosis.[24]

Further data supporting the distinction between morphea and systemic sclerosis can be found in gene array studies. Recent data have revealed differences in gene signatures between patients with morphea, LcSSc, DcSSc, and healthy controls.[26] Gene array analysis revealed evidence for four separate gene signatures, subcategorized as inflammatory, proliferative/diffuse, limited, and normal-like.[26] These distinct gene signatures reveal that although all patients with morphea and systemic sclerosis present with increased collagen deposition, they are distinct diseases.

Finally, only nine patients who presented with morphea and later developed systemic sclerosis have been reported in the literature.[27–29] Examination for sclerodactyly, Raynaud's